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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,465	10/19/2000	Peter Kufer	147-199P	3425

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EXAMINER	
CHEU, CHANGHWA J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,465	KUFER ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *22-24 and 28-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 7/23/2004 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Applicant elects group I, claims 1-24 and 27-29 with SEQ ID 75, directs to a method of using a polypeptides and antibodies for identifying binding site domain. Examiner considers both polypeptides and antibodies are within the same scope for search, therefore, restriction requirements set forth in the previous Office Action is withdrawn and the invention is regrouped as Group I (claims 1-24 and 28-33) and group II (25-27; directs to polynucleotides). This is deemed proper and ***final.***

2. Claim s 30-33 are added to the instant application.

3. Currently, claims 1-24, 28-33 are under examination. Claims 25-27 are withdrawn from further consideration.

Information Disclosure Information

The information disclosure statement filed 7/23/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been completely considered. Applicant needs to provide missing non-US patent literature for reviews.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-24, 27-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 1, line 2, "further domain" is vague and confusing. Is this domain the same as the "additional domain" recited in the same claim? It is also not clear how many domains exactly are in this biological display system? Does applicant mean the system comprises (1) binding domain; (2) additional domain and (3) further domain? Similarly, claims 9, 12, need to be clarified and be consistent.

With respect to claim 1, step (a), "an amino acid sequence that medicates anchoring of the fusion protein" is vague and indefinite. It is not clear where this anchoring amino acid located with respect to the binding domain or the additional domain or the further domain?

With respect to claim 2, line 3, "polypeptide linker comprises plural, hydrophilic, peptide-bonded amino acid" is vague and indefinite. It is not clear what applicant means "plural, hydrophilic, peptide-bonded amino acid." Similarly, claim 19 suffers the same problem.

With respect to claim 13, line 3, "a remotely detectable moiety" is vague and indefinite. It is not clear what constitutes "remotely".

With respect to claim 13, line 4, "anti-metabolite" is vague and indefinite. It is not what is the "anti-metabolite."

With respect to claims 22, line 4, "figures 6.3 to 6.10 and 7" does not comply with the Rules of Sequence set forth in the Office. Applicant needs to comply with the rules and use SEQ ID No. Similarly, claim 24, 30 and 32 suffer the same problem.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-8, 10-16, 19-21, are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al. (PNAS 1995 92: 7021) in view of Barbas et al. (PNAS 1991 88: 7978).

Mack et al. teach a method of identifying a binding site having capacity of binding to a predetermined epitope on antigen of interests, i.e. 17-1A. Mack et al. teach using a panel of E Coli. display library to periplasmic expression bispecific antibody fusion protein constructs by cloning a panel of nucleic acid molecules encoding the said domains into vectors(See Materials and Methods). The constructs comprise two main domains where one domain is the binding site domain for predetermined epitopes, and a "further domain" is linked by a "Gly-Ser" flexible linker positioned N-terminal to the binding domain (See Figure 1). The binding site domain is a pair of V_H-V_L domains (See Figure 1). The effector protein is the 17-1A which is a surface glycoprotein expressed by tumor

cells, and is rich in at least one of glutamic acid, aspartic acid, lysine, or arginine (See page 7021, left column, first paragraph). Mack et al. also teach using co-stimulatory surface molecules to increase the efficacy of the antibody-dependent cellular cytotoxicity (See page 7021, left column, first paragraph). However, Mack et al. do not specifically teach incorporating an amino acid, such as C-terminal domain of the gene III product of filamentous phage, mediating anchoring of the fusion protein to the surface of the display system. Barbas et al. teach using the C-terminal domain of the gene III protein in display library assay, e.g. mediating anchoring, to increase the sensitivity, e.g. 103- 105 fold (See Abstract, Table I). Therefore, it would have been obvious at the time the invention was made to have motivated one artisan in the art to incorporated the C-terminal domain of the gene III in the display library as taught by Barbas et al. to increase sensitivity and efficiency.

6. Claim 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al. in view of Barbas et al. and further in view of Borrebaeck et al. (US 6027930).

Both Mack and Barbas et al. references have been discussed but are silent in teaching use of a N2-domain of the gene III product of filamentous phage in the display system. Borrebaeck et al. teach an improved selection method in display library preparation. Borrebaeck et al. teach deleting part of the gene III of the phage, i.e. from nucleotides 1525 to 2646, and construct the binding domain to this vector (Col. 3, line 50- Col. 4, line 15; Result 1, Col. 4, line 47-50). Note, the deleted gene III retains the N2-terminal domain providing advantages of increasing phage infection efficiency (Col. 4, line 45-50). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Mack and Barbas et al. with the N2-domain of the deleted gene III phage product as taught by Borrebaeck et al. to further increase the detecting efficiency of the display library for identifying the binding epitopes.

7. Claims 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mack et al. in view of Barbas et al. and further in view of Lindhofer et al. (US 6551592).

Mack and Barbas et al. references have been discussed but are silent in teaching use of other co-stimulatory surface molecules, such as CD80, 86, 58 or 54. Lindhofer et al. reveal a variety of surface co-stimulatory molecules suitable for display library system, including CD40, 80, 86, 58 and 54 (Col. 5, line 4-8; claim 8). Therefore, it would have been obvious to one skilled in the art at the time the invention was made to use suitable co-stimulator molecules such as CD80, 58, 86 or 54 as taught by Lindhofer et al. since optimization of the results by different available co-stimulatory molecules merely involves routine skills in the art.

Allowable Subject Matter

8. Claims 22-24 and 28-33 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

9. The following is a statement of reasons for the indication of allowable subject matter: no prior art teaches or fairly suggests using a specific polypeptide (SEQ ID No. 75) as the complementary determining region (CDR) of an antibody for identifying binding epitopes in a display system. The closest prior art is the reference of Mack et al. which teaches using a bispecific domains in a display sytem for identifying target epitpoes. However, no specific SEQ ID No.75 as the CDR region is revealed.

Patentable Distinct Invention

SEQ ID No. **75** (as recited figure 6.10 in claims 22, 24, 30 and 32) has been searched and possesses novelty. Examiner would like to stress that the non-elected SEQ ID No. 60-74, 76-77 (recited as figures 6.3 to 6.10 and 7 in claims 22, 24, 30, 32) are patentably distinct from each other. Each is considered a patentably distinct invention. Particularly, applicant claims that those sequence relates to the CDR regions that are crucial for the antibody-antigen recognition. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and

light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (PNAS 1982 Vol 79 :1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Since there exits no continuous core structure among these SEQ ID Nos, and each SEQ ID No. has variations of amino acid within its sequence compared to others, thus each amino acid sequence is treated a distinct invention.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

October 15, 2004

LONG V. LE
SUPERVISORY PATENT EXAMINER
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10/15/04